TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference XII 861/05 sb	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/DE2004/002297	International filing date *(day/month/year)* 13.10.2004	Priority date *(day/month/year)* 13.10.2003
International Patent Classification (IPC) or national classification and IPC A61K33/24, A61P35/00		
Applicant SALAMA, Zoser, B.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 14 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DE2004/002297

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-49 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. 1-14 as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 14

because:

☒ the said international application, or the said claims Nos. 14 (in relation to industrial applicability)
relate to the following subject matter which does not require an international preliminary examination (*specify*):

Claim 14 relates to subject matter which, in the opinion of this Authority, falls under PCT Rule 67.1(iv). Consequently, no expert opinion has been established in respect of the industrial applicability of the subject matter of said claim (PCT Article 34(4)(a)(i)).

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
☐ has not been furnished
☐ does not comply with the standard

the computer readable form
☐ has not been furnished
☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-14	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-14	NO
Industrial applicability (IA)	Claims	See Box III	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

1 Reference is made to the following documents:

D1: DATABASE WPI Section Ch, Week 199815 Derwent Publications Ltd., London, GB; Class B05, AN 1998-167679 XP002321279 &; RU 2 086 261 C1 (UNIV MOSC LOMONOSOV CHEM FACULTY) 10 August 1997 (1997-08-10)

D2: TOBE M L ET AL: "Structure, activity, reactivity and solubility relationships of platinum diamine complexes" J. CLIN. HEMATOL. ONCOL. 1977, Vol. 7, No. 1, 1977, pages 114-137, XP008027197

D3: PRESNOV, M. A. ET AL: "The antitumor activity of oxoplatinum" NEOPLASMA (1985), 32(1), 73-83, 1985, XP008027150

D4: PRESNOV, M. A. ET AL: "Antitumor properties of cis-dichlorodiamminedihydroxyplatinum(IV)" IZVESTIYA AKADEMII NAUK SSSR, SERIYA BIOLOGICHESKAYA (1986), (3), 417-28, 1986, XP008027144

D5: ORR, R. M. ET AL: "Evaluation of novel platinum (II), and platinum (IV) ammine/amine complexes in L1210 murine leukemia cell lines

sensitive and resistant to cisplatin and tetraplatin" CELLULAR PHARMACOLOGY (1993), 1(1), 17-23, 1993, XP008027140

D6: BRANDON R J ET AL: "Synthesis, characterization, and properties of a group of platinum (IV) complexes." JOURNAL OF MEDICINAL CHEMISTRY. UNITED STATES JUL 1984, Vol. 27, No. 7, July 1984 (1984-07), pages 861-865, XP001184796 ISSN: 0022-2623

D7: PRESNOV, M. A. ET AL: "Cycloplatam and oxoplatin - the new antitumor platinum compounds of the second generation" ARCHIV FUER GESCHWULSTFORSCHUNG (1988), 58(1), 43-9, 1988, XP008027148

D8: KELLAND, L. R. ET AL: "Structure-activity relationships in a series of novel platinum(II) and platinum(IV) ammine-amine complexes evaluated against a panel of human ovarian carcinoma cell lines" JOURNAL OF CELLULAR PHARMACOLOGY (1992), 2(6), 331-42, 1992, XP008027138

D9: KEPRTOVÁ J ET AL: "The effect of second generation platinum cytostatics on mammalian cell proliferation." NEOPLASMA. CZECHOSLOVAKIA 1990, Vol. 37, No. 2, 1990, pages 121-129, XP008027200 ISSN: 0028-2685

D10: BLATTER E E ET AL: "Interaction of the antitumor agents cis,cis,trans PtIV(NH3)2Cl2(OH)2 and cis,cis,trans-PtIV[(CH3)2CHNH2]2Cl2(OH)2 and their reduction products with PM2 DNA." BIOCHEMISTRY. UNITED STATES 9 OCT 1984,

Vol. 23, No. 21, 9. October 1984 (1984-10-09), pages 4817-4820, XP001184794 ISSN: 0006-2960

D11: KONOVALOVA, A. L. ET AL: "Antineoplastic effect of complex platinum(IV) compounds" DOKLADY AKADEMII NAUK SSSR (1977), 234(1), 223-6 [BIOCHEM.], 1977, XP008027146

D12: YEN, TRAN CONG ET AL: "Study on potential of prolongation of survival in mice with cancers (before and after amputation) treated with cis dichlorodiamine trans-dihydroxo platinum(IV)" TAP CHI DUOC HOC (2001), (2), 19-21, 2001, XP001184196

D13: TRAN, CONG YEN ET AL: "Action of platinum(IV) complexes on sarcoma TG-180 cells in vivo" TAP CHI DUOC HOC (1998), (6), 18-20, 1998, XP001184197

D14: NGUYEN, THI QUY ET AL: "The antitumor effectiveness of a platinum(IV) compound in Swiss mice" TAP CHI DUOC HOC (1998), (3), 21-23, 1998, XP001184198

D15: AREF'EVA A K ET AL: "[Antitumor effectiveness and nephrotoxicity of oxoplatinum]" VOPROSY ONKOLOGII. USSR 1990, Vol. 36, No. 3, 1990, pages 331-334, XP008027204 ISSN: 0507-3758

D16: KELLAND L R ET AL: "A novel trans-platinum coordination complex possessing in vitro and in vivo antitumor activity." CANCER RESEARCH. UNITED STATES 1 NOV 1994, Vol. 54, No. 21, 1 November 1994 (1994-11-01), pages 5618-5622, XP001161097 ISSN: 0008-5472

D17: WO 03/066526 A (IMMCONT GMBH &; KG

PHARMOPLATIN; MELNIKOV MIKHAIL YAKOVLEVICH (RU);) 14 August 2003 (2003-08-14)

D18: EP 0 339 772 A (JOHNSON MATTHEY PLC) 2 November 1989 (1989-11-02)

D19: US 4 119 653 A (TOBE MARTIN LESLIE ET AL) 10 October 1978 (1978-10-10)

D20: VOLLANO J F ET AL: "DNA BREAKAGE BY A PERHYDRATE COMPLEX OF CIS,CIS,TRANS-PTIVCL2(NH3)2(OH)2" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, XX, XX, Vol. 106, No. 9, 1984, pages 2732-2733, XP001187504 ISSN: 0002-7863

D21: NOVAKOVA, OLGA ET AL: "DNA interactions of antitumor platinum(IV) complexes" EUROPEAN JOURNAL OF BIOCHEMISTRY (1995), 228(3), 616-24, 1995, XP008027141

D22: BRABEC V ET AL: "TETRAVALENT PLATINUM COMPLEXES CAN EXERT THEIR ANTITUMOR EFFECT VIA DIRECT REACTION WITH DNA" STUDIA BIOPHYSICA, Vol. 114, No. 1-3, 1986, pages 199-207, XP008027208 7TH CMEA (COUNCIL ON MUTUAL ECONOMIC AID) SYMPOSIUM ON BIOPHYSICS OF NUCLEIC ACIDS AND PROTEINS, BRN ISSN: 0081-6337

D23: GUTSCHE, W. ET AL: "Structure-activity relationships of active antineoplastic platinum(II) an (IV) coordination compounds" ARCHIV FUER GESCHWULSTFORSCHUNG (1989), 59(4), 233-8, 1989, XP008027147

D24: GIANDOMENICO C M ET AL: "CARBOXYLATION OF KINETICALLY INERT PLATINUM(IV) HYDROXY COMPLEXES. AN ENTREE INTO ORALLY ACTIVE

PLATINUM(IV) ANTITUMOR AGENTS" METAL CONSTRUCTION, CAMBRIDGE, GB, Vol. 34, 1995, pages 1015-1021, XP001005596

2 CLAIMS 1-14

2.1 The present application does not meet the requirements of PCT Article 33(1) because the subject matter of claims 1-14 is not inventive (PCT Article 33(3)).

Document D1 discloses (see the passages of text cited in the search report) compositions that can be administered perorally and contain 10-25 wt.% cis-diaminodichloro-trans-dihydroxy-platinum (IV) (oxoplatin), 25-55 wt.% sodium carbonate and 40-60 wt.% sodium alginate, for treating tumours, for example leukaemia, adenocarcinoma, melanoma, ovarian cancer, sarcoma and hepatoma. D1 also indicates that the orally administrable composition is not nephrotoxic.

2.2 The present application does not meet the requirements of PCT Article 33(1) because the subject matter of claims 1-14 is not inventive (PCT Article 33(3)).

D2 discloses the antitumour effect of cis-diammonium-cis-dichloro-trans-dihydroxyplatinum (IV) (oxoplatin), a compound as per claims 1-14. D2 indicates that oxoplatin is an antineoplastic agent that has a broad activity spectrum and can

be administered in a variety of ways, for example intraperitoneally, intravenously, intramuscularly and subcutaneously via bone or via the rectum; see the passages of text cited in the search report. The subject matter of claims 1-14 is therefore not inventive in relation to D2 because a person skilled in the art would choose for each administration mode the best possible galenic administration method and would produce, for example, forms of administration such as tablets, suppositories, injection solutions and/or infusion solutions according to the field of expertise.

2.3 The present application does not meet the requirements of PCT Article 33(1) because the subject matter of claims 1-14 is not inventive (PCT Article 33(3)).

Document D3 discloses (see the passages of text cited in the search report) the intraperitoneal administration of oxoplatin as an oil suspension in ground nut oil and the antitumour effect thereof on various tumours.

2.4 The present application does not meet the requirements of PCT Article 33(1) because the subject matter of claims 1-14 is not inventive (PCT Article 33(3)).

Document D4 discloses the antitumour effect of oxoplatin, a compound as per claims 1-14. D4 indicates that oxoplatin is an antineoplastic

agent that has a broad activity spectrum and can be administered in a variety of ways, for example intravenously, subcutaneously, intramuscularly, orally and rectally; see the passages of text cited in the search report. The subject matter of claims 1-14 is therefore not inventive in relation to D4. The reasons are the same as those given under point 2.2.

2.5 The present application does not meet the requirements of PCT Article 33(1) because the subject matter of claims 1-14 is not inventive (PCT Article 33(3)).

Document D5 discloses (see the passages of text cited in the search report) the antitumour effect of derivatives of cis-diammonium-cis-dichloro-trans-dihydroxyplatinum (IV); see the passages of text cited in the search report and in particular table 5. The subject matter of claims 1-14 is therefore not inventive in relation to D5.

2.6 The present application does not meet the requirements of PCT Article 33(1) because the subject matter of claims 1-14 is not inventive (PCT Article 33(3)).

Document D7 discloses (see the passages of text cited in the search report) the antitumour effect of iproplatin, a derivative of cis-diammonium-cis-dichloro-trans-dihydroxyplatinum (IV), and of oxoplatin, as well as injection solutions that

contain those agents and are used to treat tumours. The subject matter of claims 1-14 is therefore not inventive in relation to D7.

2.7 The present application does not meet the requirements of PCT Article 33(1) because the subject matter of claims 1-14 is not inventive (PCT Article 33(3)).

Document D17 discloses (see the passages of text cited in the search report) perorally administered pharmaceutical preparations (tablets) that contain cis-diammonium-cis-dichloro-trans-dihydroxyplatinum (IV), for treating tumours, for example leukaemia, adenocarcinoma, melanoma, cervical cancer, sarcoma and hepatoma. The selection of additives which are common in pharmaceuticals, for example fillers, binding agents, carrier substances and auxiliary breakdown agents, does not involve an inventive step given the lack of special technical effect thereof.

2.8 The present application does not meet the requirements of PCT Article 33(1) because the subject matter of claims 1-14 is not inventive (PCT Article 33(3)).

Documents D6, D8-D16 and D18-D24 disclose additional pharmaceutical agents which comprise cis-diammonium-cis-dichloro-trans-dihydroxyplatinum (IV), salts and/or derivatives thereof and the use thereof for treating tumours;

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

see the passages of text cited in the search report. The subject matter of claims 1-14 is therefore not inventive in relation to D6, D8-D16 and D18-D24.

3 CLAIMS 1-14

Claims 1-14 do not contain any features which, in combination with the features of any claim to which they refer, meet the PCT requirements for inventive step:

3.1 The current invention can be considered to address the problem of treating tumours and of the associated preparation of pharmaceutical agents in the form of capsules, tablets, sugar-coated tablets, suppositories, salves, injection solutions and/or infusion solutions.

3.2 It is known from D1-D24 that cis-diammonium-cis-dichloro-trans-dihydroxyplatinum (IV) and the salts and/or derivatives thereof are antineoplastic agents that have a broad activity spectrum and are used, for example, to treat cancer, for example leukaemia, adenocarcinoma, melanoma, cervical cancer, sarcoma and hepatoma. It is also known that oxoplatin and the salts and/or derivatives thereof are applied in a variety of ways, for example intravenously, subcutaneously, intramuscularly, orally and rectally, which is made possible by forms of administration such as tablets, suppositories,

injection solutions and/or infusion solutions.

3.3 The difference between the current application and documents D1-D24 lies in the preparation of alternative forms of administration. It is obvious to a person skilled in the art to use the additives which are common in pharmaceuticals according to the form of administration, for example fillers, binding agents, carrier substances, auxiliary break-down agents, etc., without thereby being inventive. In addition, the advantages of each form of administration, for example reduced nephrotoxicity, are known from D1-D5, D7, D15 and D17.

3.4 The injection or infusion solution claimed in claims 1, 4 and 14 differs from D2, for example, by the use of a carrier substance which consists of mannitol and water instead of a saline solution. The advantage of using mannitol in combination with oxoplatin (reduced nephrotoxicity) is disclosed in D15.

3.5 Similarly, an inventive step can be acknowledged in relation to claims 1-14 only when all the claimed pharmaceutical preparations provide a proven solution to the problem addressed by the invention. Since the advantages of the individual, specifically claimed forms of administration in relation to the prior art (consisting of additives which are common in pharmaceuticals, for example fillers, binding

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

agents, carrier substances, auxiliary break-down agents) has not been credibly demonstrated, an inventive step cannot be acknowledged in relation to those specifically claimed forms of administration.